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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/733,306	12/08/2000	Margaret A. Schwarz	9022.20	3192

20792 7590 11/16/2005

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EXAMINER	
EPPS FORD, JANET L	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 11/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/733,306	SCHWARZ, MARGARET A.	
	Examiner	Art Unit	
	Janet L. Epps-Ford	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-14 and 16-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-14 and 16-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11-15-2004 has been entered.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments

3. Applicant's arguments with respect to claims 1-4, 6-14, and 16-19 have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 112

4. Claims 1-2, 4, 6-12, 14, and 16-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. (Written Description).

Claims 1-2, 4, and 6-12, 14, and 16-19 are drawn to a method of facilitating vascular growth in cardiac muscle of a human subject in need of such treatment, comprising inhibiting activity of EMAP II of SEQ ID NO: 4 in said human subject by an

amount effective to stimulate vascular growth in said cardiac muscle, wherein said inhibiting step is not carried out by administering a human EMAP II antisense oligonucleotide. Therefore the scope of these claims requires "inhibiting activity of EMAP II of SEQ ID NO: 4," with the proviso that the inhibiting step does not comprise the administration of a human EMAP II antisense oligonucleotide.

Claims 2 and 12 recite methods wherein the inhibiting step is carried out by administering "a compound that specifically binds to EMAP II of SEQ ID NO: 4 to said subject," wherein SEQ ID NO: 4 is a polypeptide. Therefore the scope of claims 2 and 12 requires the administration of an undefined compound which functions to bind EMAP II, it is noted that an antibody is a species of this genus.

Claims 4 and 14 recite a method, wherein said inhibiting step is carried out by down regulating expression of an EMAP II of SEQ ID NO: 4 in said subject by an amount effective to stimulate vascular growth in said cardiac muscle. IT is noted that antisense oligonucleotides function to down regulate the expression of genes, however independent claim 1 specifically recites that the inhibiting step does not comprise the administration of antisense oligonucleotides. The specification as filed, at pages 6-7 recites a variety of classes of compounds that function to inhibit the expression of the EMAP II gene, including heterologous nucleic acid which encodes any product that inhibits expression of the EMAP II gene, such as an antisense oligonucleotide, a ribozyme, and a triplex nucleic acid. The specification further describes the administration of these heterologous nucleic acids in the form of a recombinant vector. Therefore the scope of the compounds that function to down regulate expression of an

EMAP II of SEQ ID NO: 4, includes a genus of heterologous nucleic acid molecules that encodes any product, including other genes that function to produce transcriptional factors which potentially regulate the expression of EMAP II, ribozymes, triplex nucleic acid, and any other nucleic acid inhibitor (including those that read beyond the scope of the disclosure, such as dsRNA, peptide nucleic acid, aptamers, etc.), with the exception of antisense oligonucleotides, which function to down regulate EMAP II expression. It is noted that the specification as filed does not provide any structural information regarding the various nucleic acid inhibitors or transcriptional factors which function to regulate the expression of EMAP II of SEQ ID NO: 4.

Claims 6 and 16 are drawn to method wherein the inhibiting step is carried out by administering an EMAP II receptor antagonist. The specification as filed (page 5, starting at line 4, 1st full paragraph) recites that EMAP II receptor antagonist may be identified in accordance with known techniques, but are in general analogs of EMAP II, such as EMAP II having three to five N-terminal and/or C-terminal amino acids deleted. However, Applicants provide not actual examples as to which particular amino acids should be deleted from EMAP II wherein the modified product demonstrates the ability to bind an EMAP II receptor, and further inhibit the activity of EMAP II.

With the exception of monoclonal antibodies targeting EMAP II (see pages 11-13 of the specification as filed), Applicants were not in possession of the full scope of compounds which function to inhibit the expression and/or activity of EMAP II that are required for the practice of the claimed methods. The disclosure of the monoclonal antibodies alone is not sufficient to describe the full scope of compounds, which include

a broad range of EMAP II receptor antagonist (see claim 6) that have yet to be discovered, and the generic teaching of nucleic acid inhibitors of EMAP II expression is not sufficient to describe the full scope of EMAP II expression inhibitors encompassed by the claims, which also potentially encompasses a broad range of transcription factors which function to regulate EMAP II expression.

In regards to nucleic acid based inhibitors, the limitations associated with the design and use of antisense based nucleic acid inhibitors *in vivo* also apply to other nucleic acid based inhibitors since merely designing an inhibitor based upon its ability to hybridize to a target gene or mRNA is not sufficient for determining its ability to actually function *in vivo* as an EMAP II inhibitor, and furthermore produce the corresponding phenotypic effects, namely to facilitate vascular growth in cardiac muscle of a human subject. For example expression inhibitors including for example, ribozymes, triplex forming nucleic acids must also be able to be delivered to the appropriate cardiac tissues, penetrate the plasma membrane and/or nuclear membrane, withstand enzymatic degradation, find its target nucleic acid, bind the target and simultaneously avoid non-specific binding (see Branch, 1998, cited in prior Office Action). Without further experimentation, the skilled artisan cannot predict the operability of the other species of EMAP II expression and/or activity inhibitors encompassed by the instant claims.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the

'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

MPEP 2163 states in part, "An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004) (The patent at issue claimed a method of selectively inhibiting PGHS-2 activity by administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product, however the patent did not disclose any compounds that can be used in the claimed methods. While there was a description of assays for screening compounds to identify those that inhibit the expression or activity of the PGHS-2 gene product, there was no disclosure of which peptides, polynucleotides, and small organic molecules selectively inhibit PGHS-2. The court held that "[w]ithout such disclosure, the claimed methods cannot be said to have been described.")."

The skilled artisan cannot envision the detailed structure of the encompassed EMAP II expression and/or activity inhibitors encompassed by the instant claims, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d

1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

The species of EMAP II activity inhibitor, namely monoclonal antibodies targeting EMAP II, specifically disclosed are not representative of the genus of EMAP II inhibitors because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

5. Claims 1-2, 4, 6-12, 14, and 16-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the use of monoclonal antibodies in the claimed methods comprising inhibiting the activity of EMAP II of SEQ ID NO: 4, does not reasonably provide enablement for practicing the claimed methods with any other agent. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.

The instant claims are drawn to methods of facilitating vascular growth in cardiac muscle tissue of a human subject in need of such treatment, wherein said method comprises inhibiting the activity of EMAP II of SEQ ID NO: 4, and wherein said inhibiting does not comprise the administration of antisense oligonucleotides. The methods of the claimed invention comprise the administration of an EMAP II receptor antagonist, an active agent that inhibits the activity of EMAP II of SEQ ID NO: 4, wherein said agent specifically binds EMAP II of SEQ ID NO: 4, or wherein said agent functions to down regulate the expression of EMAP II of SEQ ID NO: 4. The breadth of the instant claims reads on a broad genus of active agents, and EMAP II receptor antagonist, however the specification as filed provides only a specific example of an EMAP II monoclonal antibody, as an EMAP II inhibitor that binds EMAP II. The specification provides only a broad description of other potential inhibitors useful in their claimed methods. The

specification as filed also provides only generic guidelines for pharmaceutical formulations, delivery and dosage of active compounds, however there are no specific guidelines provided for any other agent besides the delivery of a specific EMAP II blocking antibody, see Example 1.

In regards to gene therapy based delivery methods for nucleic acid inhibitors or inhibitors produced from transcription of a transgene, the state of the art of gene therapy for the treatment of vascular disease, including cardiovascular disease, remains in the experimental phase. At the time of the instant invention, there were no clear guidelines for treating vascular disease comprising the administration of any gene known to be associated with vascularization. Some important considerations include: determining methods to detect the DNA sequence, RNA message, and gene product within the entire organism and to exert some control over its expression; selecting the appropriate vector or carrier, such that the gene therapy vector can easily be produced at a high concentration, be clinically stable, and storable for long periods of time; the vector/carrier should also demonstrate efficient cell penetration and gene incorporation in the target cell population, then either degrade within the cell or inactivate. According to Meyerson et al. (1999, see page 93), "these properties are not easily achieved, and the design of gene therapy vectors continues to be an active area of research." Additionally, Meyerson et al. describe gene therapy for therapeutic angiogenesis comprising the delivery of VEGF, however the results for a Phase I clinical trial with VEGF were inconclusive since there was no confirmation of VEGF efficacy. Meyerson

et al. (1999) concluded that whether these promising new therapies will lead to the development of organized vascular networks remains to be seen (see page 103).

Due to the broad genus of potential inhibitors encompassed by the instant claims, and the lack of description of the full scope of compounds encompassed by the claims, the skilled artisan would have to resort to *de novo* trial and error experimentation to first identify the full scope of potential inhibitors useful in the instant claims, and furthermore determine how to use these potential inhibitors *in vivo* in a human subject, with the production of the desired phenotypic effects, namely with the facilitation of vascular growth in cardiac muscle in a human subject in need of such treatment. Due to the lack of guidance in the specification as filed, and the unpredictability associated with the operability of the full scope of potential inhibitors encompassed by the claimed methods, and the need for further trial and error experimentation, it is concluded that the amount of experimentation required for the skilled artisan to practice the full scope of the claimed methods would be undue.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

7. The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting

directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

8. Claims 1-3, and 11-13 are rejected under 35 U.S.C. 102(e) as being anticipated by Schwarz et al. (US Patent No. 6,306,612 B1).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Schwarz et al. describe the use of monoclonal antibodies that specifically bind to EMAP II, for use in a method of facilitating vascular growth in a subject, e.g. in the lungs or heart of a subject (see abstract).

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 9:30 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on 517-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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Janet L. Epps-Ford
Primary Examiner
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JLE